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EDITORIAL OPEN ACCESS

Ischemic mitral regurgitation: Focusing on the imbalance of two intraventricular forces

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BACKGROUND

Ischemic mitral regurgitation (IMR) is a common complication after acute myocardial infarction (AMI) [1]. IMR represents a distinct clinical disorder from degenerative mitral regulation (MR). IMR has a broad spectrum from the acute to chronic phase. Acute MR occurs when papillary muscles suddenly rupture, which is one of the devastating mechanical complications of AMI. In contrast, chronic IMR results from progressive left ventricular remodeling late after AMI, in which lateral or inferior wall infarctions are more frequent compared with anterior wall infarctions [2].

Herein, I focus on chronic IMR and summarize the mechanism, prognosis, diagnosis, and treatments based upon literature published over the last decade.

MECHANISMS

The mitral valve leaflets coapt under the optimal balance between the two intraventricular forces: closing forces and tethering forces (Figure 1). While the closing forces control leaflet closure, the tethering forces control the leaflet opening. These forces are generated in a coordinated manner in the mitral valve apparatus: annulus, leaflets, chordae tendineae, papillary muscles, and left ventricle (LV). Imbalances between these two forces, in which the tethering forces surpass the closing forces, are responsible for IMR. LV dilatation, LV spherical deformation, papillary muscle displacement, and annular dilatation increase the tethering forces. In contrast, reduced LV contractility, dyssynchrony of the LV and papillary muscle, and reduced annular contraction can decrease the closing forces [3, 4].

With the exception of leaflet bending which is shown as a "seagull sign", leaflet abnormalities do not contribute to

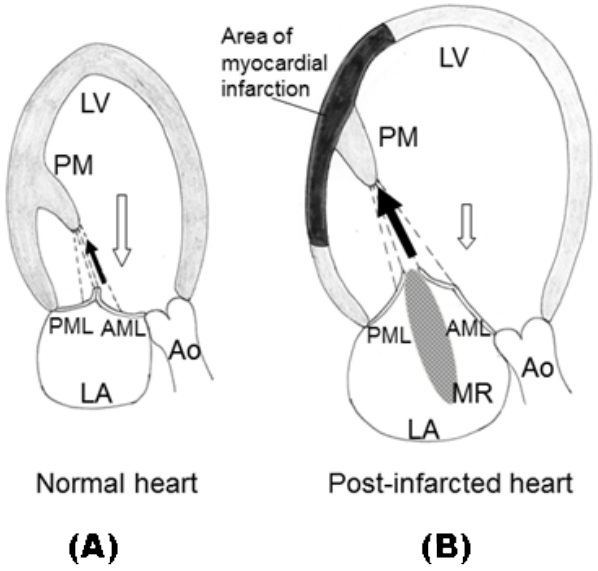

Figure 1: Schema of (A) the normal heart, and (B) the postinfarct heart.
In this schema, the white and black arrows indicate the closing force and the tethering force, respectively. The length and thickness of the arrows indicate the strength of the forces.
(A) In the normal heart, these two forces balance each other, leading to no mitral regurgitation (MR), and (B) In the postinfarct heart, imbalance between these two forces, which results from an increase in the tethering force and a relative decrease in the closing force, leads to the displacement of the leaflets into the left ventricle and malcoaptation of the mitral valve leaflets, leading to MR.
Abbreviations: Ao aorta, LA left atrium, AML anterior mitral leaflet, PML posterior mitral leaflet, PM papillary muscle

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the development of IMR. This is because IMR is regarded as a ventricular disease, not a valve disease.

PROGNOSIS

The presence of IMR worsens the clinical course of myocardial infarction [1]. The mortality risk is directly associated with increasing IMR severity. Even mild IMR can increase the risk of congestive heart failure and death [5, 6]. Grigioni et al. reported that the 5-year survival was only 29% in patients with significant IMR defined as an effective regurgitant orifice area (EROA) ≥ 0.2 cm^2 [7]. A subset of patients with EROA ≥ 0.2 cm^2 and regurgitant volume (RVol) ≥ 30 ml are at increased risk of cardiovascular events. Therefore, detection and quantification of IMR is very important for clinical decision-making and risk stratification in the chronic phase of myocardial infarction [7]. Surgical correction of IMR in addition to coronary revascularization has not provided clear evidence of improving survival rate in several studies [8-12], although inconsistent data supporting a survival advantage also exists [13-15].

DIAGNOSIS

The presence of MR is first suspected when a systolic murmur becomes audible. However, the intensity of the murmur is not associated with the severity of IMR because of reduced ventricular function [1].

The presence of IMR is easily detected by color Doppler echocardiography. When quantitating IMR severity, the PISA method is highly recommended, because it is less load-dependent. Severe IMR is defined by EROA ≥ 0.2 cm^2 or RVol ≥ 30 ml [16]. It is important to keep in mind that IMR varies dramatically in severity under different physiologic conditions or in accordance with volume loading. Furthermore, IMR tends to be underestimated echocardiographically because the regurgitant orifice in IMR is elliptical, but the formula for EROA assumes circular geometry. Thus, the assessment of IMR severity demands caution for these reasons.

TREATMENTS

The treatment for IMR has been challenging. There is no single absolute and durable treatment that resolves all cases of IMR with low rate of recurrence and long-term survival. One of the more promising treatments is the direct intervention targeting to the mechanisms of IMR, which focuses on correction of the imbalance between the decreased closing forces and the increased tethering forces. Increasing the closing forces and/or decreasing the tethering forces can facilitate effective closure of the mitral valve leading to a significant reduction in MR.

To increase the closing forces, administration of pharmacological agents, cardiac resynchronization therapy (CRT), and coronary artery revascularization are useful. To reduce the tethering forces, the therapeutic options include surgical correction of the submitral apparatus or CRT, in addition to the administration of pharmacological agents (Table 1).

Pharmacological therapies

The 2014 AHA/ACC Valvular Heart Disease Guideline recommends that standard medical therapy using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and aldosterone antagonists should be administered to patients with IMR and heart failure with reduced ejection fraction (class I, evidence level A) [17].

The aforementioned pharmacological agents can act on the left ventricle to reverse the remodeling process, which in turn decreases the tethering forces, leading to improve on the MR severity. It has been reported that the third generation β-blocker, carvedilol, significantly decreased EROA and RVol of the mitral valve in patients with chronic heart failure associated with ischemic and non-ischemic cardiomyopathy [18]. These results are linked to the reversal of the remodeling process by carvedilol with a reduction of left ventricular volume and improvement of systolic function. Therefore, β-blockers are likely to increase the closing forces as well as reduce the tethering forces.

Cardiac Resynchronization Therapy

The 2014 AHA/ACC Valvular Heart Disease Guideline recommends CRT with biventricular pacing for

Table 1: Treatment options stratified by the affected lesions at the mitral apparatus

Mitral apparatus	Treatments increasing closing force	Treatments decreasing tethering force
left ventricle	CRT Revascularization (CABG, PCI) Pharmacological agents	Revascularization (CABG, PCI) Surgery (infarction plication, ventriculoplasty) Pharmacological agents
papillary muscles	CRT	Surgery (approximation, relocation, sling)
chordae tendineae		Surgery (chordal cutting)
leaflets		Surgery (patch augmentation)
annulus	CRT	

Abbreviations: CABG coronary artery bypass graft, PCI percutaneous coronary intervention, CRT cardiac resynchronization therapy

symptomatic patients with IMR who meet the indication for device therapy (class I, evidence level A) [17].

CRT modifies the dyssynchrony of both the LV and papillary muscles, leading to an increase of the closing forces. As a result, CRT rapidly reduces the degree of MR [19–21]. Furthermore, reduction in MR with CRT is associated with improved survival and lower rate of hospitalization with heart failure due to left ventricular reverse remodeling, which also decreases the tethering forces. CRT also produces a more effective mitral valve annular contraction, resulting in the improvement of the MR [21].

Percutaneous coronary intervention

Percutaneous coronary intervention (PCI) may be beneficial for decreasing MR. Yousefzai et al. demonstrated that the severity of MR improved with isolated PCI in one-third of patients with IMR. LV reverse remodeling is responsible for the improvement in IMR after PCI [22]. A nonrandomized prospective study from Korea compared the long-term results of PCI and coronary artery bypass grafting (CABG) in IMR, and demonstrated that PCI improved MR (defined as a decrease of the EROA ≤ 0.2 cm^2) in about half of patients, which was comparable to the outcome of patients receiving CABG alone [15]. In contrast, Booher et al. reported that the severity of IMR did not change with complete multi-vessel PCI [23].

Mitral valve surgery

The 2014 ACC/AHA Valvular Heart Disease Guideline recommends that mitral valve surgery is reasonable for asymptomatic or symptomatic patients with severe IMR who are undergoing CABG or aortic valve replacement (Class IIa, evidence level C). Mitral valve repair or replacement may be considered for severely symptomatic patients with IMR (NYHA class III to IV) who have persistent symptoms despite optimal guideline determined medical therapy for heart failure (class IIb, evidence level B). Mitral valve repair may be considered for patients with moderate IMR who are undergoing, another cardiac surgery (class IIb, evidence level C) [17]. There is no class I indication for mitral valve surgery even when the patients exhibit symptoms related to heart failure with severe IMR because little data has been available to demonstrate that additional mitral valve surgery improves survival or symptoms for a prolonged period [8–12].

Several issues have been addressed regarding the optimal surgical treatments for IMR: Mitral valve repair versus replacement, the efficacy of additional subvalvular procedure, and whether or not moderate IMR should be repaired.

Mitral valve repair versus replacement

Unlike the superiority of mitral valve repair over replacement for degenerative MR, repair for IMR remains controversial. The new guideline does not make any recommendations as to which treatment will be better for patients with IMR [17].

A case-matched study demonstrated that mitral valve replacement provided better freedom from mild-to-moderate MR with a low incidence of valve-related complications and no significant difference in long-term postoperative survival and LV function [24]. I concluded that mitral valve replacement remains a feasible option for IMR.

A meta-analysis reported by Dayan et al. in 2014 revealed that mitral valve repair provided lower hospital mortality with higher recurrence of MR compared with replacement. They also showed no significant differences in survival and New York Heart Association (NYHA) class between the two surgical arms [25]. They concluded that the choice of repair or replacement depends on the predictors of recurrence and the thromboembolic risk of each patient.

Recently, the Cardiothoracic Surgical Trials Network conducted a prospective randomized control trial study comparing mitral valve repair and chordal-sparing replacement for severe IMR. This study demonstrated that the reversal of the LV reverse remodeling was accomplished equally between two surgical approaches at 12th month. Moreover, there were no significant between-group differences in the incidence of a composite of major adverse cardiac or cerebrovascular events, functional status, or quality of life at 12th month. In contrast, the higher recurrence of moderate or severe mitral regurgitation was recognized in the repair group compared with the replacement group. I concluded that replacement provides a considerably more durable treatment for mitral regurgitation and effects on long-term outcomes despite the prosthetic valve-related complications [26].

Efficacy of additional subvalvular procedures for IMR

In all of the above-mentioned studies, mitral valve repair only includes ring annuloplasty [24–26]. Isolated ring annuloplasty does not demonstrate a survival advantage for IMR with LV dysfunction, and is highly related to late recurrence of MR. Based on the modifications to the closing or tethering forces, repairs of the submitral apparatus, such as the chordae tendineae, papillary muscles and the LV, should be taken into consideration. These procedures include papillary muscle maneuvers (sling [27], approximation [28] and relocation [29]), chordal cutting [30] and reimplantation [31], infarct plication [31], and left ventriculoplasty [28]. These techniques have been proven to decrease recurrent MR, LV reverse remodeling, and improve clinical outcomes.

Whether or not moderate IMR should be repaired

In patients with moderate IMR, controversy also exists as to whether or not such patients should be treated with concomitant surgical revascularization. Penicka et al. reported that CABG alone is likely to reduce IMR in patients with significant viable myocardium and in the absence of dyssynchrony between papillary muscles [32]. The two retrospective studies demonstrated that adding mitral valve surgery to CABG provided a survival advantage over isolated CABG, with acceptable outcomes, such as reversal of LV remodeling and decreased MR [33, 34]. On the other hand, additional reports, including 1 meta-analysis [9] and 3 randomized studies [35–37], demonstrated that CABG plus ring annuloplasty provides improved LV size and ejection fraction, significant reduction of MR, and better functional status over CABG alone, but could not prove survival benefits. The most recent randomized trial reported by Smith et al. demonstrated no significant difference regarding reversal of LV remodeling at 12th month between CABG alone and CABG plus ring annuloplasty. I concluded that there is no clinical advantage of the addition of mitral valve repair to CABG within one year for these patients group, and that long-term observation could help to explain the lower degree of MR outcomes in the clinical benefits [38].

CONCLUSION

Ischemic mitral regurgitation (IMR) is a frequent complication after acute myocardial infarction (AMI) and has a worse prognosis, regardless of the severity. The mechanism of chronic IMR is the mismatch between the two intraventricular forces. IMR occurs when the tethering forces are superior to the closing forces. The diagnosis of IMR is demanding because IMR can alter its severity under different loading conditions. The treatment selection remains challenging because of variable clinical outcomes and the existence of conflicting data. Focusing on the correction of the mismatch between closing and tethering forces is one of the therapeutic options to treat IMR. Additional trials, including a randomized investigation with a long-term follow-up periods, may be required to evaluate the efficacy of surgical treatments and establish robust scientific evidence in this challenging patient population.

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Author Contributions

Masaki Hamamoto – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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